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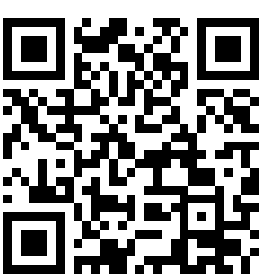

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THE EFFECT OF WHOLE BODY X-IRRADIATION ON BLOOD PRESSURE IN THE RAT

by
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ADMINISTRATIVE INFORMATION

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Dr. E. P. Cooper
Scientific Director

Captain E. B. Roth, USN
Commanding Officer and Director

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ABSTRACT

Blood pressure was measured at a peripheral and central site in the rat. Pressure at the peripheral site was determined by a tail occlusion cuff method, while central pressure was measured by aortic intubation. There was a marked decrease in blood pressure measured at the peripheral site 8 hours after the animals were exposed to 485 rads of x-rays, with a return to control values by 3 days after exposure. Aortic blood pressure, however, was not altered at this dose level. There was a mild decrease in aortic pressure 24 and 48 hours after 970 rads and a marked hypotension 8 and 24 hours following 1940 rads. The aortic blood pressure response to various stimuli was also altered after 970 rads, but not after 485 rads of x-rays. These data demonstrate that blood pressure at a peripheral site can be decreased at a dose level which does not affect central pressure. It is suggested that this differential effect in blood pressure is a result of a radiation response in peripheral circulation.

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NON-TECHNICAL SUMMARY

The Problem

The blood pressure response of animals to irradiation is one aspect of the effects of radiation on the cardiovascular system. This study describes the extent to which blood pressure, measured at a central and a peripheral site, is altered following total body exposure to x-rays.

The Findings

There was a marked decrease in blood pressure at a peripheral site 8 hours after rats were exposed to a sub-lethal dose (485 rads) of x-rays. This depression was still present 24 and 48 hours following exposure. The blood pressure returned to control values by the third day after exposure. Aortic blood pressure, however, was not altered at this dose level.

When the x-ray exposure was increased to a lethal dose (970 rads), there was a mild decrease in aortic pressure 24 and 48 hours after exposure. Following an exposure to a supra-lethal dose (1940 rads) of x-rays, animals exhibited a marked decrease in aortic pressure 8 and 24 hours post-irradiation. The aortic blood pressure response to electrical, mechanical and chemical stimuli was also decreased after exposure to 970 rads of x-rays.

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These data demonstrate that blood pressure at a peripheral site can be decreased at a dose level which does not affect central (aortic) pressure. It is suggested that this differential effect in blood pressure is a result of a radiation response in peripheral circulation.

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INTRODUCTION

Relatively little is known regarding the blood pressure response of rats to radiation exposure. Montgomery and Warren (1) used direct aortic puncture and reported a marked hypotension in anaesthetized rats within six hours of x-ray exposure to doses of 1500 r or greater. Weber and Steggerda (2) reported a decreased arterial pressure 1 to 3 hours after exposure to 600 r when pressure was measured at the tail using a plethysmographic technique. Caster et al. (3), using a tail occlusion method, observed no change in arterial pressure during the period of 3 to 12 days after exposure to 700 r.

The present study was done to determine if the fall in aortic blood pressure reported by Montgomery and Warren (1) could be detected at lower exposure doses in the non-anaesthetized rat. Pressure measurements were then made concurrently by direct aortic intubation and by a pulse detection method on the tail to determine the importance of the measurement site upon the results obtained. The blood pressure response to various stimuli was also studied as a further elaboration of the blood pressure reaction to ionizing radiation. The experiments indicate that x-ray exposure alters blood pressure at peripheral and central sites differentially in the rat during the first week post-irradiation.

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METHODS

All animals used throughout the study were adult male Sprague-Dawley rats bred from a specific pathogen-free stock at this Laboratory. The animals were individually caged and maintained in an air conditioned room with an ad libitum diet of Purina Lab Chow meal and water. An isolation gown and scrub technique were used during the handling of the animals, and no epizootic respiratory infections were observed throughout the study.

A G. E. Maxitron unit was used for radiation exposure. The machine was operated at 250 KVP, 25 ma, with a half-value layer equivalent to 2.3 mm. Cu. As measured by a Victoreen Chamber the mean dose rate (air) was 15.4 r/minute except for the initial radiation study. In the initial study the dose rate was 123 r/minute. A factor of 0.97 was used to convert the roentgen dose, measured in a paraffin phantom, to rad dose. In a preliminary lethality study the LD50/30 value was 805 rads for rats of the same sex, strain, age and conditions of exposure as those used in the present study. The doses used in this study were 485 rads, 970 rads and 1940 rads, which correspond to a sublethal, lethal and supra-lethal dose, respectively.

The aortic blood pressure was measured by means of an indwelling aortic catheter which was connected to a Statham P23AA strain gauge

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pressure transducer at the time of measurement. Pressure measurements were recorded on a Grass Model 5 Polygraph. The strain gauge was calibrated before the measurement of each animal and the calibration was rechecked after each test. The technique for aortic intubation was based upon the method described by Still and collaborators (4, 5) using young adult male rats. Based on weight curves and clinical observations, recovery from the operation was complete in seven days. The yield of successful preparations for blood pressure measurements by this technique was approximately 75%. Animals have been maintained as long as nine months following aortic intubation, with longer maintenance apparently possible. The use of an indwelling catheter permits the measurement of direct aortic blood pressure without interference from anaesthesia or other drugs.

Systolic blood pressure in the tail was determined with a Continuous Systolic Monitor (Beckman-Spinco Instrument Co.) using a 5/8 inch wide Gaertner-type occlusion cuff. The detection of pressure pulses, obtained by a miniature condenser microphone pickup (Infraton-F, Beckman-Spinco) located on the tail, initiates recurrent small increases in cuff pressure above a regulated rate of pressure bleed-off. When pulse detection is blocked, pressure input is stopped until the cuff pressure has dropped below systolic pressure and the pulse is again detected. In this manner the pressure is monitored approximately every third pulse or nearly continuously.

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Several modifications of the Continuous Systolic Monitor were made in order to adapt it for use with the rat. An increased sensitivity was necessary for pulse detection in the tail and was accomplished by minor circuit modification within the Monitor and the addition of a pre-amplification stage (Tektronix Low Level D.C. Unit, Type 122). Pressure recordings from the Monitor were displayed on a Grass Polygraph by means of a Statham strain gauge pressure transducer (Model P23AC) which was connected to the Monitor. The strain gauge pressure transducer was calibrated with a mercury manometer before each animal was measured and calibration was rechecked after each test. An oscilloscope was used to monitor the pulse signal from the Infraton so that attachment of the sensing element on the tail could be standardized with respect to signal amplitude. The oscilloscope tracings were also recorded on the Grass Polygraph along with the pressure recordings for the elimination of pressure records corresponding to occasional artifacts of respiration and movement detected by the Infraton sensing element.

EXPERIMENTAL RESULTS

Observations Related to the Period of Radiation Exposure:

Blood pressure was studied during and immediately following irradiation to detect the earliest change which might occur in non-anaesthetized animals. The aortic intubation method was used to determine blood pressure.

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Preliminary to this study it was necessary to determine the number of eight-hour adaptation sessions required to bring the animals to a steady state with respect to blood pressure and pulse rate during confinement to the radiation exposure chambers. It was found that the pulse rate and blood pressure attained their lowest values and remained stable after two adaptation sessions of eight hours duration for each session. The mean pulse rate and blood pressure obtained under these conditions was approximately 380/minute and 135 mm. Hg, respectively. It was also found that adpated animals required approximately sixty minutes to reach a steady state after being confined to the holders.

As a result of the preliminary experiments, each animal was adapted to confinement in a holder made of two vertical Lucite end plates connected by Lucite rods to form a cylindrical enclosure for the rat. Both the length and diameter of the holder were adjustable, so that the animal was allowed some freedom of movement for the maintenance of a comfortable position. The adaptation series consisted of two eight-hour sessions during the week preceding x-ray exposure. Exposure to x-rays and all measurements in this study were made while the animals were in the holders and without the use of anaesthesia.

Continuous blood pressure recordings commenced 1 1/2 to 2 hours prior to the onset of radiation. This period was utilized to adapt the animals to the physical surroundings and noises associated with

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the x-ray machine. Most animals reached a steady state, with respect to blood pressure, within the first half-hour, and all animals reached a steady state within one hour. Sham-irradiated controls were placed behind a lead shield in the x-ray exposure room and their blood pressures were measured concurrently with those of the irradiated animals.

The results are summarized in Fig. 1. The mean blood pressure of animals exposed to 970 rads did not differ markedly from that of controls for the first eight hours following the onset of irradiation. Animals exposed to 1940 rads showed a marked hypotension which commenced about four hours after the onset of irradiation and continued throughout the remainder of the eight-hour test period. On the day following irradiation, continuous aortic blood pressure measurements were made on the same animals over a one hour period. The mean blood pressure of animals that had been exposed to 1940 rads was significantly lower ($p \leq 0.01$) than that of the sham-irradiated controls (Fig. 1). Animals that had been exposed to 970 rads were also significantly lower ($p \leq 0.05$) than controls.

Aortic Blood Pressure Following Irradiation:

In view of the hypotension apparent at 24 hours after exposure, aortic blood pressure measurements were made to determine if the changes in central pressure persisted during the first three days post-irradiation.

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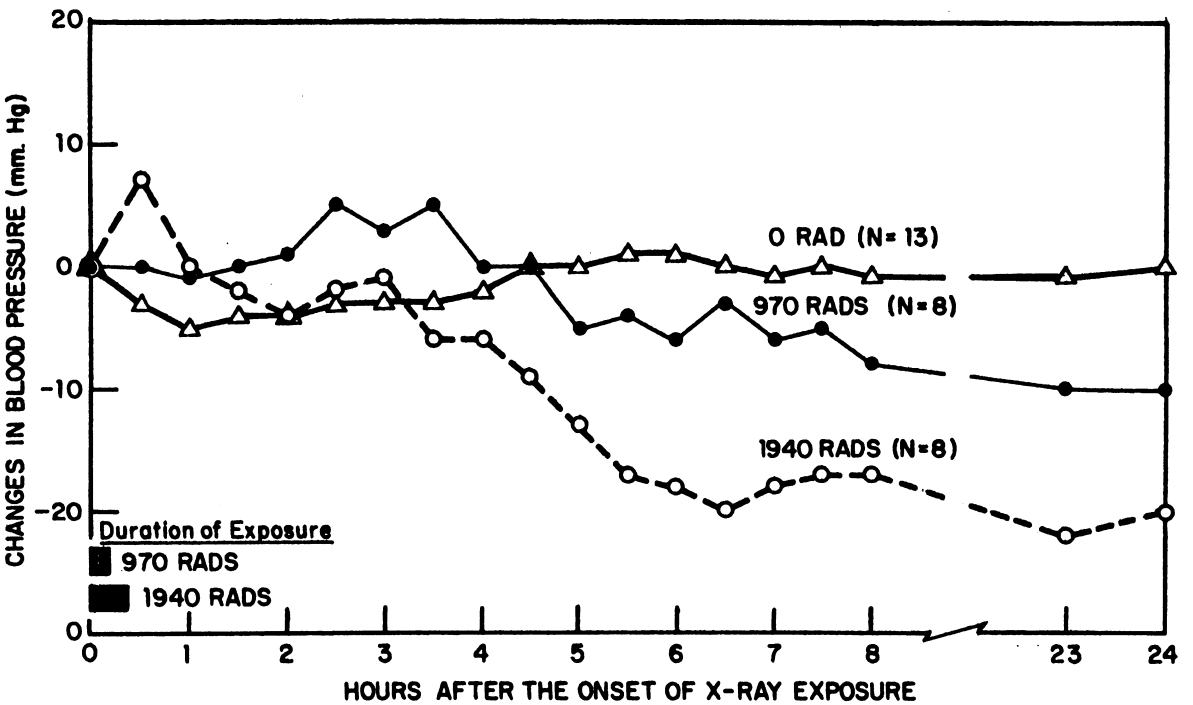

Fig. 1 Change in blood pressure from pre-irradiation values. The average standard error for controls was 4.1 mm. Hg. Blood pressure was determined by the aortic intubation method.

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The animals were subjected to six two-hour adaptation periods prior to the two-hour test session. Irradiation and all measurements were made without anaesthesia while the animals were confined in the holders. During the test session, the first hour after the animals were placed in the holders was used as an adaptation period, and the mean values of the next one-half hour were accepted as steady state values. Blood pressure measurements were made on all animals prior to exposure. Measurements on each animal were restricted to one pre-irradiation test and one post-irradiation test.

The results are summarized in Fig. 2. The mean blood pressure of animals exposed to 485 rads did not differ significantly from controls for the first 3 days following irradiation. Animals exposed to 970 rads exhibited a very mild hypotension one and two days following irradiation and a mild hypertension three days post-irradiation. Although the degree of hypotension was relatively small after 970 rads, the findings corroborated the previous experiment regarding the response to 970 rads both in direction and magnitude; the response was also consistent with the pattern at a higher exposure dose. For purposes of comparison, data from the previous study at 8 and 24 hours after exposure to 1940 rads are plotted in Fig. 2. As previously described, there was a marked hypotension 8 and 24 hours following irradiation. No attempt was made to measure blood pressure in this group beyond twenty-four hours after exposure since it was likely that blood pressure changes relating directly to death would be encountered.

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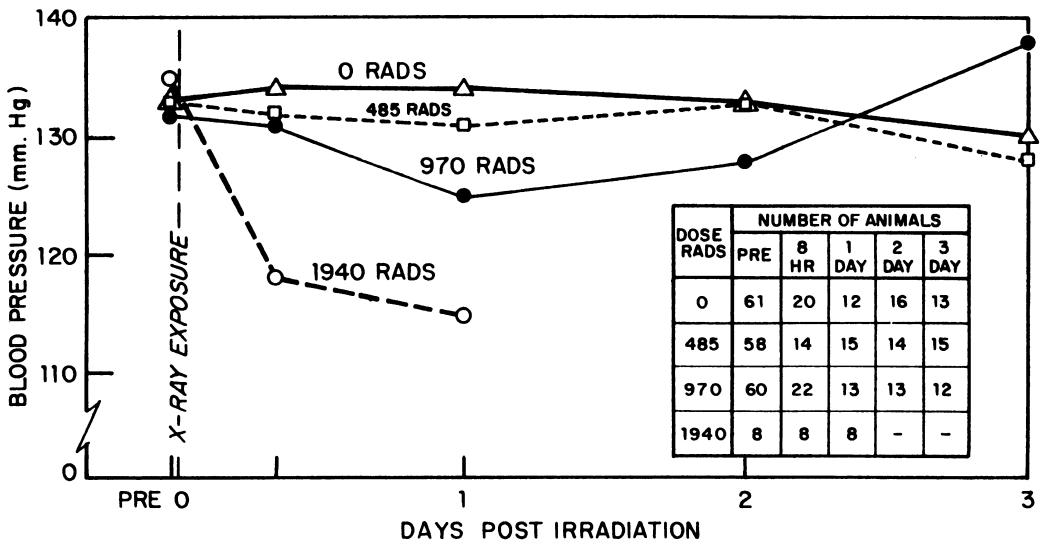

DOSE RADS	NUMBER OF ANIMALS				
	PRE	8 HR	1 DAY	2 DAY	3 DAY
0	61	20	12	16	13
485	58	14	15	14	15
970	60	22	13	13	12
1940	8	8	8	-	-

Fig. 2 Aortic blood pressure during the first three days following X-ray exposure. The average standard deviation for the pre-irradiation means was 11.2 mm. Hg.

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Responsivity of Aortic Blood Pressure Following Irradiation:

The responsivity of blood pressure in the aortic intubated rat to various stimuli was determined in order to characterize further the cardiovascular response in irradiated animals. The experimental procedures for this study were the same as in the previous study except for the introduction of the stimulus. Different groups of animals were used for each stimulus, and each animal was subjected to a single test.

Mechanical, chemical and electrical stimuli were utilized. The mechanical stimulus consisted of prodding with a blunt probe at the shoulder girdle of the animal for ten seconds. The chemical stimulus was 0.2 micrograms of nor-epinephrine infused intravenously into a vena cava catheter. This catheter was implanted during the same operation for aortic intubation by essentially the same technique used for aortic intubation. Administration of the drug was standardized to produce a blood pressure response of approximately + 40 mm. Hg. The electrical stimulus, from a Model S-4 Grass Stimulator, was applied to a wet electrode at the base of the tail. The characteristics of the electrical stimulus needed to produce a blood pressure response of approximately + 100 mm. Hg were as follows: 32 volts D.C., positive square wave, 60 cycles/seconds, 10 milliseconds pulse duration and five seconds stimulation time.

A summary of the results is shown in Fig. 3. Animals exposed to 970 rads exhibited responses which were less than those of controls at

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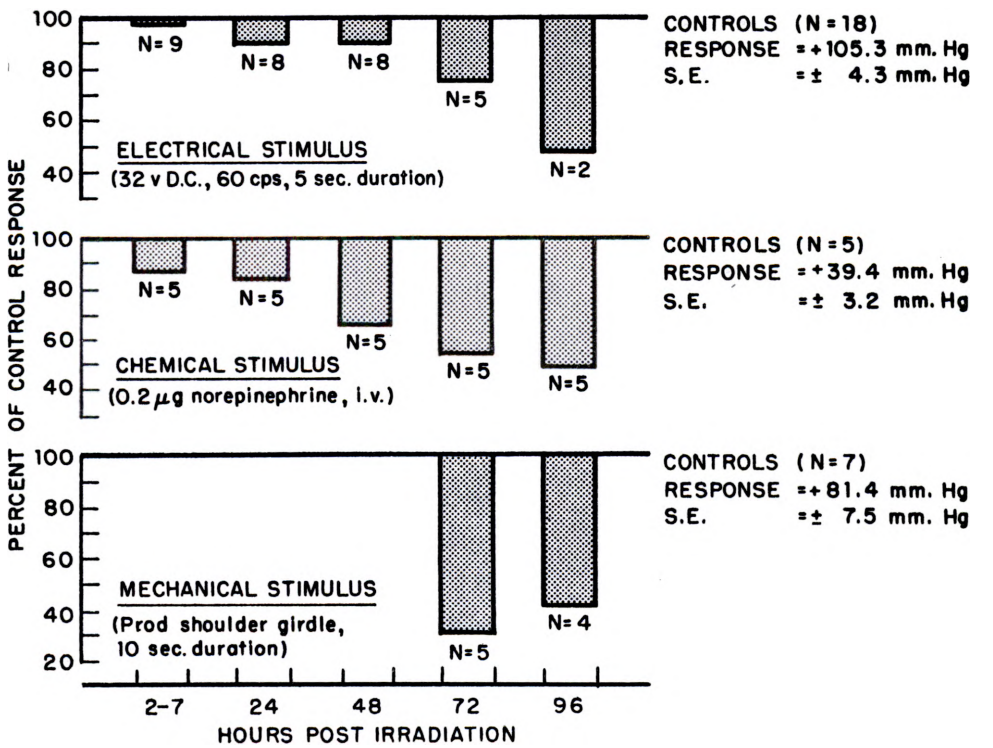

Fig. 3 Percent of control blood pressure response to electrical, chemical and mechanical stimuli during the first 96 hours following X-irradiation (970 rads).

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nearly all test points post-irradiation with all three stimuli. The mean blood pressure response of the sham-irradiated control group to the electrical stimulus was + 105.3 mm. Hg, while the group exposed to 970 rads exhibited a progressive marked decrease in responsivity with time post-irradiation. By 96 hours post-irradiation the blood pressure response of the irradiated group was only 50% of the control response. This same general pattern was seen following the chemical stimulus. The sham-irradiated control group exhibited a + 39.4 mm. Hg blood pressure rise to 0.2 micrograms (0.1 ml) of nor-epinephrine i.v., while there was a progressive decrease in responsivity in the irradiated group. As was the case following the electrical stimulus, the response of the irradiated group to the chemical stimulus 96 hours post-irradiation was only 50% of the control response. A decrease in blood pressure responsivity of irradiated animals was also demonstrated following a mechanical stimulus at 72 and 96 hours following irradiation. The blood pressure response to electrical stimulus in animals exposed to 485 rads (not shown) did not differ significantly from responses in controls during the first week following irradiation.

Simultaneous Measurements of Aortic and Tail Blood Pressures Following Irradiation:

The possibility was considered that discrepancies regarding blood pressure changes in the irradiated rat among previous investigators may be the result of regional differences in response - viz.

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central pressure changes versus peripheral pressure changes. Therefore, a study was designed to determine both the aortic blood pressure and the tail, or peripheral, blood pressure simultaneously.

A series of preliminary experiments was done to establish the relationship between blood pressure values obtained by the aortic intubation and tail occlusion methods when measured simultaneously in anaesthetized animals. The results are summarized in Fig. 4. Each value is the mean of a five minute test session. A relationship exists between the pressures obtained by the two methods which can be described by the linear equation $y = mx + b$, where y is the aortic blood pressure, x the tail blood pressure, m the slope and b the y intercept. A best fit line was established by the method of least squares, and a slope (m) of 0.9 and y intercept (b) of 15 were determined. From the values of m and b it was found that over the pressure range of 80 to 150 mm. Hg by the aortic intubation method, the corresponding pressure range by the tail occlusion method was 72 to 150 mm. Hg. The maximum difference of only 8 mm. Hg occurred at the lower end of the pressure range under the conditions used in the present study.

In contrast to the previous studies, anaesthesia was employed to avoid artifacts produced by animal movement which could interfere with measurements of tail blood pressure. Nembutal, 35 mg./kg. i.p., was used as the anaesthetic agent. This level of anaesthesia was found to

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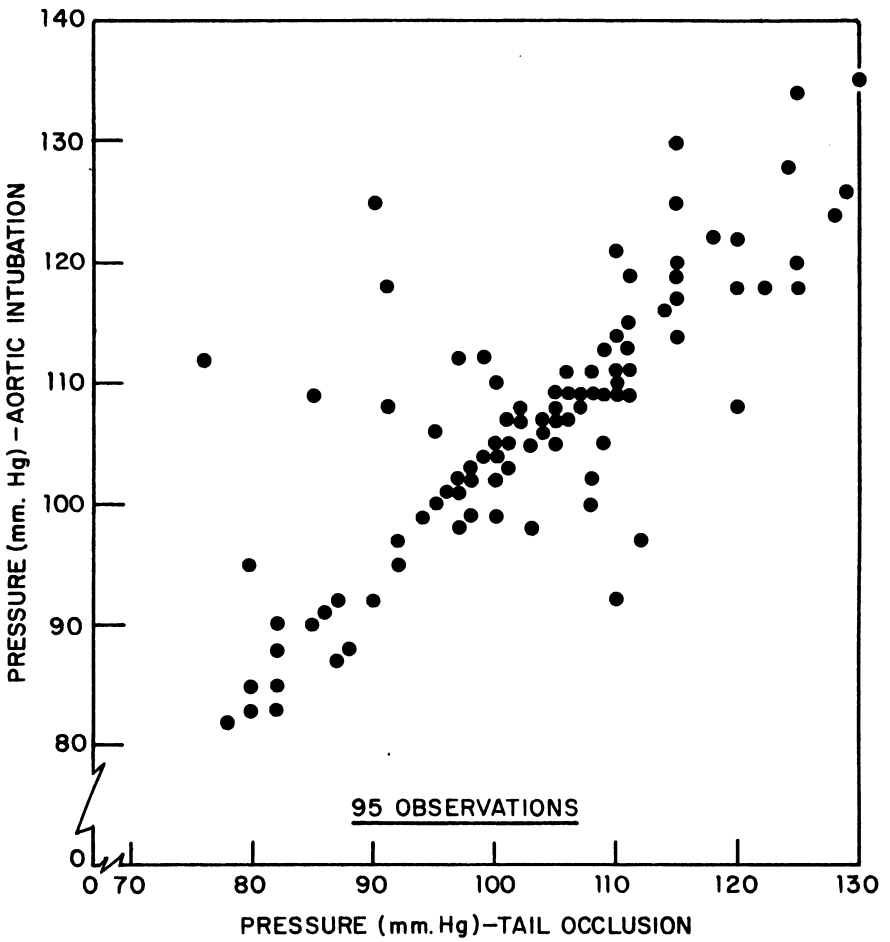

Fig. 4 Values for systolic blood pressure recorded simultaneously by the aortic intubation and tail occlusion methods.

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give reproducible blood pressure values and response patterns within the population of 37 animals used. The blood pressure range was 103 to 112 mm. Hg at 30 minutes after injection of Nembutal.

Blood pressure measurements were made prior to irradiation and over the first 10 days post-irradiation at the time intervals indicated in Fig. 5. The blood pressure value of each animal is based on the mean of a five minute recording thirty minutes after the administration of anaesthesia. The aortic and tail blood pressure measurements were determined simultaneously.

Prior to irradiation the mean aortic blood pressures for control and experimental groups were 108 and 107 mm. Hg, respectively, and the simultaneous mean tail blood pressures for the two groups were 105 and 104 mm. Hg. Following these measurements the experimental animals were exposed to 485 rads and control animals were sham-irradiated. Aortic and tail blood pressure measurements were made once on each animal within the 10-day period following exposure or sham-exposure. The results are summarized in Fig. 5. Aortic blood pressure of animals exposed to 485 rads did not differ significantly from controls over the time period tested, and corroborated the previous experiment regarding the response to 485 rads. There was, however, a marked fall in tail blood pressure. The maximum depression occurred eight hours post-irradiation with a return to the range of control values by the third day after irradiation. From the third to the tenth day following

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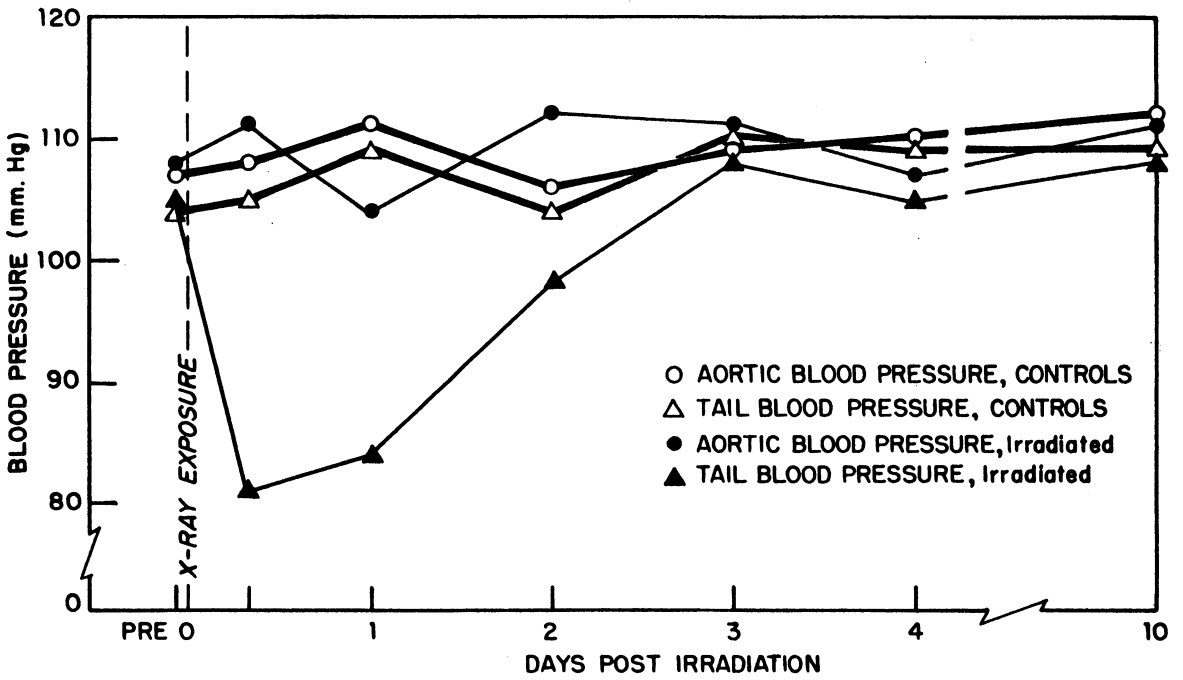

Fig. 5 Simultaneous measurements of aortic and tail blood pressures for the first 10 days following X irradiation (485 rads). Total number of irradiated animals was 30 (5 rats/test point), and the number of control animals was 7 (one rat/test point, except day 2 which consisted of 2 animals). The average standard deviation for pre-irradiation means was 7.3 mm. Hg for aortic blood pressure and 8.2 mm. Hg for blood pressure measured at the tail.

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irradiation, the tail blood pressure of the irradiated group did not differ from that of the control group.

DISCUSSION

The results of this study indicate that there was a marked decrease in blood pressure measured at a peripheral site following a sublethal (485 rads) exposure to x-rays although central (aortic) pressure was maintained. When the dose was increased to 970 rads the central pressure was somewhat impaired with a mild hypotension occurring 24 and 48 hours post-irradiation. The results at a higher dose level (1940 rads) suggest that compensatory mechanisms were unable to maintain central blood pressure with a resultant marked hypotension which commenced four hours after the onset of irradiation and persisted for at least 24 hours following irradiation.

It is of interest that the aortic blood pressure responsivity to stimuli is not altered after exposure to 485 rads but is modified after 970 rads of x-rays. This would appear to add corroborative evidence regarding the stability of central pressure at a lower radiation dose in contrast to the peripheral pressure changes at this dose. The change in responsivity is not simply a reflection of hypotension at the higher dose since it occurred at a time when the hypotension was no longer present.

The present observations and reports in the literature suggest the hypothesis that the reduction in peripheral blood pressure at the sublethal dose reflects a radiation response in peripheral vascularity.

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Prosser et al. (6) and Painter and Moore (7) have observed a histamine-like shock syndrome with hypotension in rabbits after mid-lethal doses of x-rays. Histamine has been found in rat plasma following irradiation and has been correlated with hypotension (2). Haley et al. (8) were able to demonstrate that a vasodepressor material, which caused a profound peripheral vascular paralysis, was released into the circulation of rats during the first week following 600r of x-rays. The vasodepressor action was manifested by decreased sensitivity of precapillary sphincters and terminal arterioles to epinephrine and a partial paralysis of capillary bed vessels. A similar reaction was obtained by injecting blood, serum or plasma from irradiated donors into non-irradiated rats. The present study may reflect a similar phenomenon with the reduction of peripheral blood pressure at a comparable dose level and a decreased sensitivity to nor-epinephrine at a higher dose level.

The reduction of pressure at peripheral sites concurrent with no apparent decrease in central pressure suggests compensatory mechanisms which lead to a steeper pressure gradient from central to peripheral sites. The stability of central pressure at a dose level which alters pressure at peripheral sites indicates an effective compensatory mechanism. The fall in central pressure after higher radiation doses suggests that those mechanisms were unable to compensate fully for the reduction of peripheral pressure with a resultant decrease of aortic

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pressure as the radiation dose was increased. The reduction of aortic pressure following a high radiation dose could conceivably be the result of a derangement of central nervous system function. Montgomery and Warren (1) have suggested that the cause of the immediate hypotension is a depression of the central nervous system. Their evidence to support this hypothesis is based on the failure of spinal-transected rats to exhibit hypotension following radiation exposure to 1500r. Although CNS derangement could conceivably cause hypotension at high radiation doses through a breakdown of CNS regulation of cardiovascular compensatory mechanisms, it does not appear to explain the pattern at lower radiation exposure doses where there is a fall in peripheral pressure with a stable aortic pressure.

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SUMMARY

Blood pressure was measured at two sites in the rat. Pressure as measured at the tail exhibited a marked decrease 8 hours after X-ray exposure to 485 rads, with a return to control values by 3 days after irradiation. Aortic blood pressure, however, was not altered at this dose level. There was a mild decrease in aortic pressure 24 and 48 hours after 970 rads and a marked hypotension eight and 24 hours following 1940 rads. The aortic blood pressure reponse to various stimuli was also altered after 970 rads but not after 485 rads of X rays. These data demonstrate that blood pressure at a peripheral site can be decreased at a dose level which does not affect central (aortic) pressure. It is suggested that this differential effect in blood pressure is a result of a radiation response in peripheral circulation.

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THE EFFECT OF WHOLE BODY X IRRADIATION ON BLOOD PRESSURE IN THE RAT by R.D. Phillips and D.J. Kimeldorf 28 p. illus. 8 refs.
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2. Circulatory system - Effects of radiation.
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